La Prensa Medica Argentina

Research Article

Autoimmune hemolytic anemia in chronic lymphocytic leukemia

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Rec date: Dec 24, 2013 **Acc date:** Mar 19, 2014 **Pub date:** Mar 21, 2014

Abstract:

Background: Chronic lymphocytic leukemia (CLL) is a malignant proliferation of mature, differentiated B-lymphocytes, frequently associated with autoimmune hemolytic anemia (AIHA). The effect of this complication in the clinical outcome and survival of patients with CLL is controversial. The aim of study was to evaluate the prevalence of AIHA in our patients with CLL and how this complication influences the patient's survival.

Methods: We studied 84 patients with CLL hospitalized in the Clinic of Hematology from Craiova (Romania) between 2007 and 2012. The diagnosis of CLL was made according to the national protocol. The diagnosis of AIHA was based on the presence of unexplained Hb level < 10 g/dL or Ht < 30%, positive Coombs test (DAT) and the presence of one or more indirect markers of hemolysis: reticulocytosis, increased serum lactate dehydrogenase or bilirubin levels. Classical prognostic indicators (age, sex, clinical stage, blood lymphocyte count, blood lymphocyte doubling time, bone marrow infiltration) for autoimmune cytopenia and overall survival in patients with CLL with or without AIHA were evaluated.

Results and conclusions: The prevalence of AIHA was of 23% correlated with classical prognostic indicators: high blood lymphocyte count, short blood lymphocyte doubling time, advanced clinical stage, higher bone marrow infiltration. No significant statistical differences were observed in the overall survival between patients with and without AIHA in patients with CLL.

Key words:

CLL; AIHA; Survival

Introduction:

Chronic lymphocytic leukemia (CLL) is a malignant proliferation of mature, differentiated lymphocytes, mostly of B-cell origin, frequently associated with autoimmune cytopenia (autoimmune hemolytic anemia and immune thrombocytopenia). Autoimmune hemolytic anemia (AIHA), defined as an acquired hemolytic anemia in which the destruction of erythrocytes is mediated by anti-erythrocyte auto antibodies, occurs in 5-38% of patients with CLL [1,2,3]. The effect of autoimmune hemolytic anemia on the clinical outcome and survival of patients with CLL is controversial [4,5]. Some studies evaluated the prognostic significance of the origin of cytopenia and concluding that cytopenia due to bone marrow failure is associated with poor prognosis whereas immune cytopenia is not an adverse prognostic marker [1,3,5] The prognosis in CLL is based on classical prognostic indicators (clinical stages, blood lymphocyte count, lymphocytes morphology in peripheral blood, blood lymphocyte doubling time, bone marrow infiltration degree) and new prognostic markers such as: genetic abnormalities, expression of specific proteins in or on CLL cells (i.e, CD38, CD49d, ZAP-70) and the IGHV mutation status of a CLL clone [6,7,8]. The aim of the study was to evaluate the prevalence of autoimmune hemolytic anemia in our patients with CLL and how this complication influences the patient's survival.

Methods:

We studied 84 patients with CLL hospitalized in the Clinic of Hematology from Craiova () between 2007 and 2012 (informed consent obtained). The patients were distributed by age, sex, environmental medium, Binet staging. The diagnosis of CLL was made according to the national protocol and whenever possible the diagnosis was confirmed by flowcytometry. The diagnosis of autoimmune hemolytic anemia was based on the presence of unexplained hemoglobin level < 10 g/dL or hematocrit < 30%, positive Coombs test and the presence of one or more indirect markers of hemolysis: reticulocytosis, increased serum lactate dehydrogenase or bilirubin levels. Patients were confirmed as having stage C Binet infiltrative when either hemoglobin level < 10 g/dL or platelet count to < 100.000/mm3, with no positive Coombs test and no indirect signs of hemolysis. Other biological parameters determined were: leukocyte count and leukocyte formula, peripheral blood smear, bone marrow smear, erythrocytes sedimentation rate, serum β2microglobuline. The chemotherapy regimens were: chlorambucil + Prednisone, CVP-regimen (Cyclophosphamide + Oncovin + Prednisone), Fludarabine alone, RFC-regimen (Rituximab + Fludarabine + Cyclophosphamide) or alemtuzumab (anti CD52 monoclonal antibody). The treatment of autoimmune hemolytic anemia were: corticosteroids alone or corticosteroids and cyclophosphamide/vincristine. Statistical analysis was performed and a P value ≤ 0.05 was considered significant. Classical prognostic indicators: clinical stages, blood lymphocyte count, blood lymphocyte doubling time, bone marrow infiltration degree were evaluated. The new prognostic markers such as genetic abnormalities, expression of specific proteins in or on CLL cells and the IGHV mutation status of a CLL clone could not be evaluated in our clinic.

Results:

The median age of the patients with CLL was of 65 years; the sex ratio M/F=1.62, revealed a male predominance. Repartition on the stage of disease showed: CLL-stage A = 23 patients, CLL-stage B = 30 patients, CLL-stage C = 31 patients. Immuno phenotyping revealed B phenotype in 80 cases and T phenotype in 4 cases. Autoimmune hemolytic anemia was present in twenty patients (23%). AIHA appeared in one case (5%) two years before the diagnosis of CLL, at the time of diagnosis in four cases (20%) and during the evolution of CLL in fifteen cases (75%) One patient had Evans syndrome, associated autoimmune hemolytic anemia and immune thrombocytopenia

(hemoglobin value = 8g/dl, reticulocytes = 3%, test Coombs positive, LDH = 384 u/L, indirect bilirubin = 1.8mg/dl, unexplained fall platelet count = 69.000/ mm3, normal megakaryocytes in bone marrow). Two patients had the Coombs test positive without evidence of hemolysis. The patients with CLL were treated with chlorambucil + Prednisone = 16 cases, CVP = 19 cases, Fludarabine alone = 10 cases, RFC = 8 cases, alemtuzumab = 4 cases. Two patients (10%) developed AHAI after chlorambucil treatment and one (5%) after Fludarabine. The patients with CLL-stage C and autoimmune hemolytic anemia were treated with corticosteroids alone in 2 cases and corticosteroids and chemotherapy (cyclophosphamide or vincristine) in two cases, and switched from stage C in stage A in two cases and stage B in two cases. The patients with C stage infiltrative (27 cases) were treated with chemotherapy and in two cases switched from stage C to stage B was realised. Overall survival was of 6.9 years in patients with CLL and AIHA versus 8.2 years in patients with CLL without AIHA. Characteristics of patients with CLL and AIHA compared with patients with CLL without AIHA are in table 1.

	CLL+ AHAI (20 patients)	CLL without AHAI (64 patients)	p
Median age (years)	67	72	NS
Male (%)	70	60	NS
Hb x 109/L (range: 11.2-16.5)	9.4	10.6	< 0.05
WBC x 109/L (range: 4.00-10.00)	31.4	29.1	NS
Abs. Ly count x 109/ L(1.18-3.74)	20.6	19.4	< 0.05
Ly doubling time < 12mo%	35	23	< 0.05
Plt countx109/L(range: 150-370)	102	143	NS
Bone marrow infiltration %	61	83	< 0.05
LDH > 214 UI/L %	75	72	NS
Binet stage			
A	3	20	NS
B	13	17	NS
C	4	27	< 0.05
Overall survival, years	6.9	8,2	NS

Table 1: Characteristics of patients with CLL+ AIHA versus CLL-without AIHA

Disussion:

The prevalence of autoimmune hemolytic anemia in patients with CLL in our study was of 23% compared to the data in literature, in which the occurrence of autoimmune cytopenia (autoimmune hemolytic anemia or immune thrombocytopenia) had been reported as ranging from 5% to 38%, depending on the definition of autoimmune cytopenia, criteria selection, length of follow-up [2,9].

Classically clinical characteristics associated with autoimmune cytopenia are old age, male sex, a high lymphocyte count, short lymphocyte doubling time and advanced clinical stage [1,3,10]. In our study, a high absolute lymphocyte count, short lymphocyte doubling time, advanced clinical stage (stage C) were significantly associated with autoimmune hemolytic anemia occurrence.

The mechanism of autoimmune hemolytic anemia in CLL is still unclear; erythrocytes autoantibodies, imbalances in immunosurveillance mechanisms, altered T-regulatory cells function and treatment with purine analogs and chlorambucil are considered to play a role as initiators of AIHA [11,12,13,14]. The addition of cyclophosphamide to fludarabine may have a protective role on the occurrence of AIHA [15]. In our study, two patients (10%) developed AHAI after chlorambucil treatment and one (5%) after fludarabine alone.

The effect of autoimmune hemolytic anemia in the clinical outcome and overal survival of patients with CLL is controversial. Some studies revealed a poor survival in patients with CLL and AIHA than other patients with CLL, and other studies showed that the development of autoimmune hemolytic anemia anytime during the evolution of the disease (at diagnosis, during or after therapy) did not significantly influence the overall survival [1,3,16,17]. On the other hand, the evaluation of the prognostic significance by the origin of cytopenia (immune or infiltrative) concludes that cytopenia due to bone marrow failure has a poor prognosis while autoimmune cytopenia is not an adverse prognostic factor [4,5] The patients with stage C - immune of disease had longer survival than patients with stage C - infiltrative disease, because of the response to therapy (a large proportion of patients with CLL - stage C immune did respond to steroids and shifted to stage A, whereas only a small percentage of patients with stage C infiltrative did respond to chemotherapy and shifted in an early stage of disease) [16]. In our study, the patients with CLL-stage C and autoimmune hemolytic anemia were treated with corticosteroids alone in two cases and corticosteroids and chemotherapy (cyclophosphamide or vincristine) in two cases, and switched from stage C in stage A in two cases and stage B in two cases. The patients with C stage infiltrative (27 cases) were treated with chemotherapy and in two cases the switch from stage C to stage B was realised. Overall survival was of 6.9 years in patients with CLL and AIHA versus 8.2 years in patients with CLL without AIHA.

Conclusion:

In our study, the prevalence of autoimmune hemolytic anemia was of 23%, correlated with classical prognostic indicators: high blood lymphocyte count, short blood lymphocyte doubling time, advanced clinical stage, higher bone marrow infiltration. No statistically significant differences were observed in the overall survival between patients with and without autoimmune hemolytic anemia in patients with CLL, median survival being of 6.9 years in patients with CLL and AIHA versus 8.2 years in patients with CLL without AIHA.

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